METAL-CATALYZED INTRAMOLECULAR CYCLIZATION OF 2-DIAZO-4-(4-INDOLYL)-3-OXOBUTANOIC ACID ESTERS

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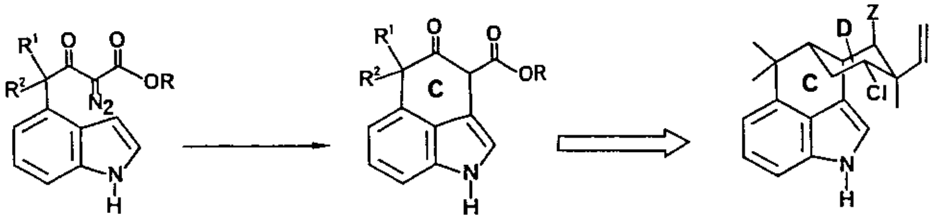
Abstract —— $Rh_2(OAc)_4$-catalyzed decomposition of 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters (1) leads to indoles 3, whereas $Pd(OAc)_2$-catalyzed reaction of 1 gives indoles 2 with C-ring.

Intramolecular C-H bond insertion by diazoketones has become an excellent methodology to construct highly substituted cyclic ketones.[1,2] The recent development has, however, been focused on the aliphatic C-H bond insertion with carbenes and carbenoids generated by metal-catalyzed decomposition of diazo compounds. The intramolecular aromatic C-H bond insertion should be as well an interesting entry to cyclic system fused with aromatic ring. For this reaction, there have been a few examples known with acid catalysis.[1]

In the course of our study on the synthesis of 4-substituted indoles and related alkaloids, we examined whether 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters (1) led to the indoles 2 with C-ring via C-H bond insertion.[3]

Copper-catalyzed reaction of ethyl diazoacetate with indole is well known to afford 3-indoleacetic acid ester.[4] Accordingly, we expected that the diazoketone 1 would lead to a tricyclic compound 2, which should be a key intermediate with functionalities for further transformations toward ergot and clavine alkaloids, and also toward a new class of alkaloids such as hapalindoles.[5]



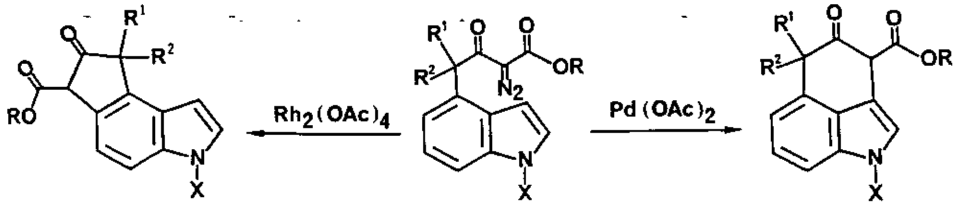
1

2

hapalindole A (Z= -N=C)
B (Z= -NCS)

A solution of the diazoketone 1a (100 mg) in toluene (2 ml) was heated in the presence of $Cu(acac)_2$ (2 mg) at 80°C for 6 h. After chromatographic separation, a tricyclic compound was obtained in ca. 20% yield. It was not the desired one 2a but a compound 3a derived from the intramolecular C-H bond insertion at the 5-position of 1a. The structure of 3a was determined by nmr(400MHz), ms, ir and elemental analyses.[6] In place of $Cu(acac)_2$, $Rh_2(OAc)_4$ was next used for the cyclization of 1a. The Rh-catalyzed reaction occurred smoothly at room temperature and the tricyclic compound 3a was produced in 89% yield after 30 min. For the Rh-catalyzed reaction of 1a, a variety of medium such as methanol, benzene and their mixtures were surveyed, but the results were not essentially different.

On the other hand, the Pd-catalyzed reaction of 1a gave completely different result from the case of Cu or Rh. When a solution of 1a (281 mg) and $Pd(OAc)_2$ (10 mg) in methanol (5 mL) at 0°C for 45 min, the desired cyclization product 2a was obtained in 71 % yield together with a slight amount of 3a (<1%). The physical properties of 2a were cited in



3 1 2

Table 1. Metal-catalyzed cyclization of 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters (1).

1						2			3		
	R	R^1	R^2	X	Catalyst		Yield(%)	Mp (°C)		Yield(%)	Mp (°C)
(1a)	Et	H	H	H	$Rh_2(OAc)_4$	(2a)	<1	110(dec)	(3a)	89	110-113
					$Pd(OAc)_2$		71			<1	
(1b)	Et	H	H	Tosyl	$Rh_2(OAc)_4$	(2b)	0	---	(3b)	61	155.5-8.5
					$Pd(OAc)_2$		--	---		--	
(1c)	Me	H	H	$PhCH_2$-	$Rh_2(OAc)_4$	(2c)	0	---	(3c)	86	120-1.5
					$Pd(OAc)_2$		0	---		51	
(1d)	Et	Me	Me	H	$Rh_2(OAc)_4$	(2d)	0		(3d)	87	oil
					$Pd(OAc)_2$		77	143-4.5		17	
(1e)	Et	i-Bu	H	H	$Rh_2(OAc)_4$	(2e)	1		(3e)	73	oil
					$Pd(OAc)_2$		55	86(dec)		0	

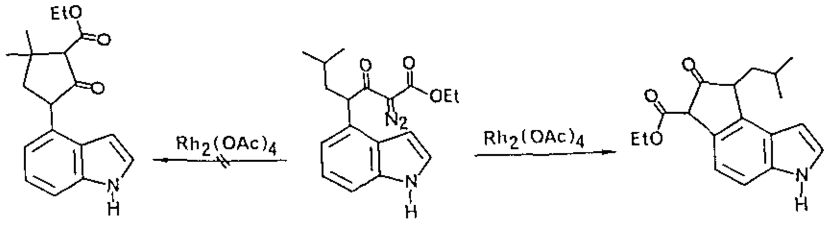
Note.[7] The other Pd-catalyst such as $PdCl_2(PhCN)_2$ and $(PdCl)_2(\pi\text{-}C_3H_5)_2$ was also moderately active for the transformation of 1a to 2a (40-60% yield). The older method with acid catalyst,[1] $HClO_4$, CF_3CO_2H, BF_3, and so on, was unsuccessful for the present purpose.

The Pd- and Rh-catalyzed reactions were further investigated for the diazoketones 1b-e with various substituents and the results were summarized in Table I. The results of 1b and 1c showed that the cyclization at the 3-position forming 2 was significantly affected by the N-substituent of indole 1. Similar trend in the reactivity of indoles is well recognized for electrophilic substitutions such as Vilsmeier-Haack reaction and Friedel-Crafts reaction.[8] A carbocationic species was strongly suggested to participate in the Pd-catalyzed reaction of 1. The following fact supported the suggestion: aprotic solvent such as CH_2Cl_2, benzene, and ethyl acetate was far less effective than protic solvent such as methanol for the $Pd(OAc)_2$-catalyzed cyclization of 1. The cyclization of 1 to 2 was formal C-H bond insertion of a carbene (carbenoid) and was likely an electrophilic substitution toward the indole skeleton.

The Rh-catalyzed intramolecular aliphatic C-H bond insertion has recently been found to prefer substantially for five-membered ring formation.[2a,b] A plausible mechanism seemed to include a six-membered ring transition state comprising of rhodium carbenoid and the hydrogen atom that is to be transfered.[2b] The Rh-catalyzed cyclization of 1 to 3 might proceed in a similar fashion. On the other hand, the cyclization to 2 would require a seven-membered transition state, which was probably less stable than the six-membered one mentioned above. This seemed a reason for the substantial preference for formation of 3 in the Rh-catalyzed reaction of 1.

The diazoketone 1e was formally capable of undergoing the aliphatic C-H bond insertion to yield a cyclopentanone 4. The $Rh_2(OAc)_4$-catalyzed reaction of 1e gave, however, 3e without 4. This fact was likely due to difference between acidity of hydrogen on the aromatic ring and that of saturated carbon.

A sterically congested diazoketone 1d gave also 2d and 3d, though the regioselectivity was somewhat blunt. It is worth to point out that the tricyclic compound 2d possesses a basic



4 1e 3e

skeleton with functionalities enough to build up the D-ring of hapalindoles.

The results described here can be summarized as follows: (i) transition metal such as Cu(II), Pd(II), and Rh(II) effectively catalyzed generation of the carbenoids from 1, to cause the intramolecular aromatic C-H bond insertion without addition to the C=C double bond of aromatic ring, which frequently leads to ring-expansion products and (ii) the regiochemistry of the C-H bond insertion extremely depended on the metal catalyst used.

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(4) S. S. Nametkin, N. N. Melnikov, and K. S. Bokarev, Zhur. Priklad. Khim., 1956, 29, 459.

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(6) Enol form. NMR($CDCl_3$) δ1.47(t, J=7.1Hz, 3H), 3.73(s, 2H), 4.43(q, J=7.1Hz, 2H), 6.45(ddd, J=3.0, 2.0, and 0.7Hz, 1H), 7.21(dd, J=3.0 and 2.8Hz, 1H), 7.31(dd, J=8.4 and 0.7Hz, 1H), 7.56(d, J=8.4Hz, 1H), 8.03-8.21(m, 1H), 10.94-11.12(m, 1H)ppm. IR(KBr) 3427, 1638, 1590, and 1485 cm^{-1}. Mass(m/z,%) 243(M^+, 17), 197(100), 169(34), and 141(96). Anal. Calcd.($C_{14}H_{13}NO_3$): C,69.12; H,5.39; N,5.76. Found: C,68.75; H,5.32; N,5.63.

(7) Enol form. NMR($CDCl_3$) δ1.46(t, J=7.1Hz, 3H), 4.13(s with fine coupling, 2H), 4.41(q, J=7.1Hz, 2H), 6.84(ddd, J=6.8, 2.3, and 1.0Hz, 1H), 7.07(dd, J=1.0 and 0.9Hz, 1H), 7.09(dd, J=8.1 and 0.9Hz, 1H), 7.14(dd, J=8.1 and 0.9Hz, 1H), 7.62-7.76(m, 1H), and 12.83(s, 1H). IR(KBr) 3370, 1647, and 1627 cm^{-1}. Mass (m/z,%) 243(M^+), 197(100), 169(45), and 141(56). High Mass(m/z) 243.0889 (er= -0.5mmu)(M^+, $C_{14}H_{13}NO_3$).

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